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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/455,486	12/06/99	AFAR	D 1703-011.US2

HM12/0412

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	11

DATE MAILED: 04/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/455,486	AFAR ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *4-21 and 24-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

The Election filed January 19, 2001 (Paper No. 9) in response to the Office Action of December 15, 2000 is acknowledged and has been entered. Claims 1-43 are pending in the application and Claims 4-21, 24-43 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-3, 22-23 are pending and are under consideration.

Applicant's election with traverse of Group I, claims 1-3, 22-23 in Paper No 9 is acknowledged. The traversal is on the ground(s) that the inventions have not been shown to be independent and the examination of all groups would not impose a serious burden on the examiner. Applicants further argue that at the very least, a search of the art relating to Groups I, III, and IV could be completed with a single search. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in Paper No. 8.

As to the question of burden of search, the inventions are classified differently, necessitating different searches in the US Patent shoes. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The isolated STEAP-2 polypeptide of SEQ ID NO: 6 (Claims 1-3, 22-23) is not disclosed either in the specification or the claims of the parent application, 09/323873. If applicant disagrees with any rejection of claims 1-3, 22-23 set forth in this office action based on examiner's establishment of a priority date of December 6, 1999 for the instant claims in application serial number 09/455,486, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Specification

The specification is objected to for the following reason: The specification on page 1 (i.e. instead of page 50) should be amended to reflect the priority status of the present application, for example:

This application is a C.I.P. of US Application No. 09/323873, filed June, 1, 1999.

The specification is further objected to on pages 34, 36-37, 40,46-47,49 for improper disclosure of nucleotide sequences. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). This definition sets forth limits, in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required.

Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. (see MPEP 2422).

The disclosure is further objected to (page 36, line 37; pages 46-47,48) because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The specification is further objected to on page 44 (lines 16-31) for reciting "STRAP-1" as it appears that the specification is solely drawn to STEAP polynucleotides and polypeptides.

The Brief Description of the Figures is objected to for the following reasons:

1) Figures of sequence listings (i.e. Figure 1A) should be separately labeled when they are displayed on multiple pages as indicated by the draftsman.

2) The description of Figures 5-7 recite "STEAP", however the figures indicate "STRAP".

3) Reference to Figure 11 (page 7, line 15) should be omitted since there is no respective Figure 11.

4) The description of Figure 11A should indicate the respective SEQ ID NOs: for STEAP polypeptides 1-4. The disclosure is further objected to because it contains an embedded

hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

5) The description of Figure 11B recites "STEAP", however the figure indicates "STRAP".

6) The description of Figures 11B-D are objected to for reciting "XX" in reference to specific SEQ ID NOs:.

7) The description of Figures 12, 13, and 14 are objected to for improper disclosure of sequence listings without respective SEQ ID NOs:.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22 and 23 are rejected as vague for reciting "expressing a STEAP-2 protein comprising (or comprising an immunogenic portion) a STEAP-2 protein" as it is unclear what is expressing the STEAP-2 protein. This rejection can be obviated by clearly directing the claims to the elected invention- the STEAP-2 protein, i.e. "a vaccine composition for the treatment of cancer comprising a STEAP-2 protein".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 22-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make/ and or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to an isolated STEAP-2 protein having an amino acid sequence of SEQ ID NO: 6. The claims are further drawn to an isolated polypeptide of at least 8 contiguous amino acids of the protein of claim 1 and or an isolated polypeptide comprising an amino acid sequence which is at least 90% identical to the amino acid sequence of SEQ ID NO: 6 over its entire length. The claims are further drawn to a vaccine composition for the treatment of cancer expressing a STEAP-2 protein.

However, the claims are not enabled because the specification provides insufficient guidance and or objective evidence for one of skill in the art to predictably make/use the

polypeptide(s) without undue experimentation. Furthermore, the specification provides insufficient guidance and or objective evidence that any vaccine composition comprising a STEAP-2 protein would effectively treat cancer with any predictability.

1. With regards to cancer treatment using a vaccine comprising a STEAP-2 protein, the specification provides no exemplification of or guidance on how to use the claimed vaccine formulation or antigen for activity immunotherapy in humans. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease, however there is nothing in the specification to indicate that such a vaccine would effectively treat cancer. Bellone et al. (Immunology Today, v20 (10), 1999, pp.457-462) summarize the current state of the art of peptide immunotherapy including clinical trials where "there is usually a poor correlation between induction of specific T-cells and the clinical responses" (page 457, 2nd column). Bellone et al. further teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) risk of generating tumor escape mutants, and (4) risk of autoimmune reactions (page 461, Box 1). Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental

problem in drug discovery for cancer is that the model systems are not predictive. In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1). All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer. In the instant case, the claims are so broadly drawn, the guidance is so limited, and the art is so unpredictable that the skilled artisan is presented with a multitude of alternatives with no guidance as to which will enable use of the invention as claimed.

2. Furthermore, with regards to the enablement of the isolated STEAP-2 polypeptide of SEQ ID NO: 6, it would not be predictable that one of skill in the art would know how to use the product with any predictability (i.e. for in-vivo use of a vaccine as recited above). As another example of the unpredictability of the use of the protein, the specification teaches that determining the status of STEAP expression patterns in an individual may be used to diagnose cancer and may provide prognostic information useful in defining appropriate therapeutic options. However, those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide- such as the amino acids of SEQ ID NO: 6. For example, Alberts et al.

(Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, one of skill in the art would not be able to predict if the expression of the STEAP-2 protein was in fact translated. Moreover, the specification teaches (page 12, lines 9-14) that STEAP-2 is expressed in *both* normal human prostate and prostate cancer. Thus, it would be unpredictable that protein expression would be useful for diagnostic and or prognostic purposes as the specification fails to differentiate a quantitative difference between cancerous and normal prostate tissue. Essentially, the teachings in the specification are an invitation to

experiment wherein the artisan is invited to elaborate a functional use for a putative polypeptide.

3. With regards to fragments of the STEAP-2 polypeptide, the specification provides insufficient guidance and or objective evidence to use and or make the invention as broadly claimed which includes a whole universe of polypeptides which have the 8 contiguous amino acids as well as a whole universe of polypeptides with 90% identity to SEQ ID NO.6. The specification teaches that the invention provides STEAP polypeptides comprising biologically active fragments of the STEAP amino acid sequence. These include polypeptides which exhibit properties of a STEAP-1 protein, such as the ability to elicit the generation of antibodies, and or allelic variants with conservative amino acid substitutions or those (page 18, lines 22-25) that contain a radical departure from the sequence, such as a non-conservative substitution, truncation, insertion or frame shift which do not perform the same biological functions. One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any polypeptide fragment with sequence homology to STEAP-2 with or without the biological properties representative of what is claimed, and applicant has not enabled all of these types of modified proteins because it has not been shown that these modified proteins are capable of functioning as that which is being disclosed. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio.

111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all fragments with sequence similarity to the amino acid sequence shown in Fig. 9 (SEQ ID NO. 6).

In view of the teachings above, and the lack of guidance and or exemplification in the specification, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

If applicant were able to overcome the 112 1st paragraph enablement rejection of above, the following claims would still be rejected.

Claims 2-3, 23 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated STEAP-2 protein having an amino acid sequence shown in Figure 9 (SEQ ID NO: 6), does not reasonably provide enablement for an isolated polypeptide of at least 8 contiguous amino acids and or an isolated polypeptide comprising an amino acid sequence which is at least 90% identical to SEQ ID NO. 6. Furthermore, Claim 23 is rejected, because the specification, while being enabling for a vaccine composition for the treatment of cancer comprising a STEAP-2 protein and a physiologically acceptable carrier, does not reasonably provide enablement for a vaccine composition for the treatment of a cancer expressing a STEAP-2 protein comprising an immunogenic portion of a STEAP-2 protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to an isolated polypeptide of at least 8 contiguous amino acids of the protein of claim 1 and or an isolated polypeptide comprising an amino acid sequence which is at least 90% identical to the amino acid sequence in SEQ ID NO.6. The claims are further drawn to a vaccine composition for the treatment of a cancer expressing a STEAP-2 protein comprising an immunogenic portion of a STEAP-2 protein.

This includes a whole universe of polypeptides which have the 8 contiguous amino acids as well as a whole universe of polypeptides with 90% identity to SEQ ID NO.6.

The specification teaches (page 18) that the invention provides STEAP polypeptides comprising biologically active fragments of the STEAP amino acid sequence. These include polypeptides which exhibit properties of a STEAP protein, such as the ability to elicit the generation of antibodies, and or allelic variants with conservative amino acid substitutions or those that contain a radical departure from the sequence, such as a non-conservative substitution, truncation, insertion or frame shift which do not perform the same biological functions. With regards to immunogenic fragments, the specification teaches (page 48) the top 5 ranking peptide candidates which are *predicted* to the be most tightly bound to HLA Class I on the cell surface and thus represents the best immunogenic targets for T-Cell recognition.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any polypeptide fragment with sequence homology to STEAP-2 with or without the biological properties representative of what is claimed, and applicant has not enabled all of these types of modified proteins because it has not been shown that these modified proteins are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid

sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Furthermore, with regards to immunogenic fragments, it would not be possible to determine with any predictability whether the antibodies produced from such fragments actually bind to STEAP-2 polypeptides or to a STEAP-2 polypeptide of SEQ ID NO: 6. It is well known in the art that when using synthetic amino acid sequences as immunogens to develop antibodies, one cannot be certain how well exposed such a peptide is nor how immunogenic it is. Furthermore, this does not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides or synthetic antigens cannot effectively substitute for the natural tertiary and quarterary structure of a protein in a physiological situation.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all of the polypeptides which have the 8 contiguous amino acids as well as all of the polypeptides with 90% identity to SEQ ID NO.6.

Therefore, in view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim 2 is rejected under 35 U.S.C. 102(e) as being anticipated by Lal et al. (US Patent No. 6048970, May 1998, - see attached sequence listing).

The claim is drawn to an isolated polypeptide of at least 8 contiguous amino acids of the protein of claim 1.

Lal et al. teach an isolated polypeptide of at least 8 contiguous amino acids of the protein of claim 1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
April 9, 2001

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